The Examiner maintains the position that Isomura et al. teaches a bisphosphonate composition for oral administration with anti-bone resorption activity useful in treating metastatic osteocarcinoma that includes the compound of the present invention. The Examiner acknowledges that Isomura et al. does not teach the claimed compound in a method of treating bone lesions associated with multiple myeloma and myeloma itself, nor the claimed effective dose.

However, the Examiner states that Shipman et al. teaches that bisphosphonates have anti-bone resorption activity, anti-tumor activity, apoptosis inducing activity, and may be useful in treating multiple myeloma. Thus, the Examiner maintains that one of ordinary skill in the art would have been motivated to optimize the dosage range and use the claimed bisphosphonate in a composition to treat multiple myeloma and bone lesions associated with multiple myeloma.

Applicants' response

Applicants note that basis for this rejection is the Examiner's contention that Isomura et al. teaches bisphosphonate compositions for oral administration and with anti-bone resorption activity. However, as the Examiner acknowledges, Isomura et al. does not teach the specific claimed compound for use in the treatment of bone lesions associated with multiple myeloma and myeloma itself, nor the claimed effective dose.

The Examiner goes on to state that Shipman et al. teaches that bisphosphonates have anti-bone resorption activity, anti-tumor activity, apoptosis inducing activity, and may be useful in treating multiple myeloma. Thus, the Examiner maintains that one of ordinary skill in the art would have been motivated to optimize the dosage range and use the claimed bisphosphonate in a composition to treat multiple myeloma and bone lesions associated with multiple myeloma.

Thus, the Examiner is arguing that Isomura et al. teaches the bisphosphonate composition of the present invention, and that Shipman et al. teaches the use of such compounds for the treatment of bone lesions associated with multiple myeloma and myeloma itself.

In response, Applicants respectfully assert that the present invention is not obvious over Isomura et al. in view of Shipman et al. Indeed, contrary to the Examiner's position, Shipman et al. does not teach or make obvious the use of the bisphosphonate of the present invention in both the suppression of bone resorption accompanying multiple myeloma and the inhibition of multiple myeloma. Shipman et al. merely suggests that some bisphosphonates may have apoptosis-inducing activity. Indeed, while Shipman et al. notes that some bisphosphonates have been shown to inhibit myeloma cell proliferation and induce apoptosis, they also clearly state that "a number of important questions remain unclear, including whether bisphosphonates have a direct effect on primary myeloma cells, whether these effects occur *in vivo*, and whether these compounds are more or less effective when used in combination with other chemotherapeutic agents....This is a topic that warrants further investigation." (page 136, lines 4-14).

Thus, at the most, Shipman et al. makes it obvious to try certain bisphosphonates in the dual treatment of bone lesions and multiple myeloma. Use of an obvious to try standard has been held to be impermissible by the courts (*In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Shipman et al. only makes it obvious to explore a new technology that seems to be a promising field of experimentation. There was no expectation that bisphosphonates would work for the purpose recited in the claims of the pending application.

Further as set forth in the first Response Under 37 C.F.R. §1.116, filed on June 27, 2002, in this application and incorporated herein, there was a number of peer-reviewed journal articles

that suggested bisphosphonates could not be used in the treatment of multiple myeloma at the time Shipman et al. was published.

Indeed, at the time of the present invention was developed, and Shipman et al. was published, a further peer-reviewed journal article provided an equally strong suggestion that bisphosphonates could not be used to treat multiple myelomas.

Dallas et al. (*Blood* 93(5):1697-1706 (March 1999)) was published only four months after Shipman et al.[1] Therein, the authors show that two bisphosphonates, ibandronate and risedronate, had no effect on the total myeloma cell burden in a murine model of human myeloma bone disease.

Dallas et al. evaluated the direct anti-tumor effects of ibandronate, a potent bisphosphonate, using a murine model of human myeloma disease. They found no direct anti-tumor activity. While ibandronate did show good effects on the inhibition of osteolytic lesions (Figures 2, 3 and 4), no effect on tumor burden was found (Tables 1 and 2). Furthermore, no changes in the levels of M-protein (serum IgG2b), which is a tumor marker, were found (Figure 6).

Furthermore, experiments similar to those conducted by Shipman et al. and Aparicio et al. were performed by Dallas et al., wherein the effects on *in vitro* growth and apoptosis of the 5TGM1 myeloma cell line were investigated. As shown in Figure 3, and described in the paragraph bridging pages 1703 and 1704, using physiological ranges of two different bisphosphonates, the investigators found "no significant effect with ibandronate or risedronate on

[1] A copy of Dallas et al. is enclosed.

the total number of myeloma cells...in culture" (page 1704, first column, lines 9-10). Thus, Dallas et al. clearly show that a cytotoxic effect cannot be expected at an acceptable *in vivo* drug concentration.

The authors concluded that "our results support those of a number of human clinical trials in which the effects of bisphosphonates on survival have been reported. Lahtinen et al., Laakso et al. and McCloskey et al. showed no improvement in survival in myeloma patients treated with clodronate. Similar results were reported by Brincker et al. using oral pamidronate" (page 1705, first column, lines 1-6 of the last paragraph).

Thus, while one report may have suggested that bisphosphonates could be used to induce apoptosis of myeloma cells, another report clearly suggested the contrary. As a result, it would only have been obvious to try the experiments described in the present application. That the compound of the present invention could be used to successfully treat bone lesions and multiple myeloma was not made obvious by the prior art.

In light of these comments, Applicants respectfully request reconsideration and withdrawal of the rejection.

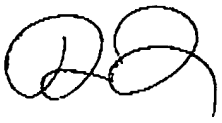
II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

SECOND RESPONSE UNDER 37 C.F.R. §1.116 Q64929
U.S. Appln. No. 09/869,122

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Drew Hissong
Registration No. 44,765

SUGHRUE MION, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3213
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

Date: August 22, 2002